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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,552	09/22/2003	Johannes Bartholomaeus	029310.50777CP	6176

23911 7590 10/29/2010

CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
10/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,552	BARTHOLOMAEUS ET AL.	
	Examiner	Art Unit	
	S. TRAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,9-26 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,9-26 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/06/10 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Rejections - 35 USC § 103

Claims 1-4, 6, 7, 9-26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. US 4,690,927, in view of Mok et al., and Addicks et al. US 5,041,430, and Bergamini et al. US 5,597,560 or Bodley et al. US 5,679,660.

Voss teaches a pharmaceutical dosage form comprising mixture of diclofenac sodium and salt of codeine in a weight ratio of about 1:1 to 3:1 (abstract; and claims 1-3). The dosage is suitable for oral administration in the form of granule, dragee, tablet, layered tablet, and capsule (column 2, lines 11-64). The two active substances can be formulated in separate layers in a tablet (ID). The final dosage form can be film coated with hydroxypropylmethyl cellulose (example 1).

Voss is only deficient in the sense that Voss does not teach the use of tramadol.

Mok teaches combination of tramadol and diclofenac useful for the treatment of pain (abstract).

Thus, it would have been obvious to one of ordinary skill in the art to optimize the dosage form of Voss to include the combination of tramadol and diclofenac in view of the teachings of Mok to obtain the claimed invention. This is because Mok teaches that combination of tramadol and diclofenac provides the best pain relief, because Mok teaches that combination of tramadol and diclofenac is known in the art and has low side effects (see abstract), and because Voss teaches the desirability of combining

diclofenac with an opioid analgesic compound to achieve a more intense therapeutic effect but eliminating side effects (column 2, lines 5-10).

Voss further does not explicitly teach the separation of two active agents.

Addicks teaches a dosage form comprising combination of at least two active agents, wherein the active agents are separated by a coating layer to minimize physical contact between the active agents to prevent chemical interaction (columns 4-5). Thus, it would have been obvious to one of ordinary skill in the art to include the separating layer between the diclofenac and the codeine to obtain a more stable composition. This is because Addicks teaches a dosage form suitable for the delivery of at least two active agents that are known to have potential for chemical interaction (column 3, lines 65 through column 4), and because diclofenac is known in the art to exhibit interaction with quite a number of active agents. See for example Bergamini et al. at column 7, lines 20-30; and Bodley et al.

Claims 1-4, 6, 7, 9-26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffa US 5,516,803, in view of Mok et al., and Addicks et al. US 5,041,430 and, and Bergamini et al. US 5,597,560 or Bodley et al. US 5,679,660.

Raffa teaches a composition comprising combination of tramadol and an NSAID (abstract; and column 3, lines 15-59). NSAID includes diclofenac (column 4, lines 29-37).

It is noted that Raffa teaches diclofenac among a number of NSAID.

However, combination of diclofenac and tramadol is known in the art. See Mok's abstract for example. Mok teaches a combination of tramadol and diclofenac for the treatment of pain.

Thus, it would have been obvious to one of ordinary skill in the art to optimize the composition of Raffa to include the combination of tramadol and diclofenac in view of the teachings of Mok to obtain the claimed invention. This is because Mok teaches that combination of tramadol and diclofenac provides the best pain relief, because Mok teaches that combination of tramadol and diclofenac is known in the art and has low side effects (see abstract), and because Raffa suggest combining tramadol and NSAID that could include diclofenac.

Raffa does not teach the separation of two active agents.

Addicks teaches a dosage form comprising combination of at least two active agents, wherein the active agents are separated by a coating layer to minimize physical contact between the active agents to prevent chemical interaction (columns 4-5). Thus, it would have been obvious to one of ordinary skill in the art to include the separating layer between the combination of active agents such as tramadol and diclofenac to obtain a more stable composition. This is because Addicks teaches dosage forms suitable for the delivery of at least two active agents that are known to have potential for chemical interaction (column 3, lines 65 through column 4), and because diclofenac is known in the art to exhibit interaction with quite a number of active agents. See for example Bergamini et al. at column 7, lines 20-30; and Bodley et al.

Response to Arguments

Applicant's arguments filed 10/06/10 have been fully considered but they are not persuasive.

Applicant argues that Voss is silent as to any unfavorable physical or chemical interaction between diclofenac and tramadol and does not disclose discrete subunits for the active ingredients. In all of the specific examples provided in Voss et al., the active agents are mixed together.

In response to Applicant's arguments however, the Examiner noted that Voss is cited for the teachings within the four-wall patent, Voss cannot be limited to the examples alone. The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain. *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983). Applicant's attention is called to column 2, lines 46-54 for the specific teaching of the two active agents are separately prepared and compressed into two distinct layers.

Applicant argues that Raffa does not explicitly disclose the presently claimed combination of tramadol or a pharmaceutically acceptable salt thereof with diclofenac or a pharmaceutically salt thereof. Moreover, Raffa, like Voss et al., provides no indication that there might be any problem arising from the direct combination of tramadol and diclofenac.

However, in response to Applicant's argument that Raffa does not teach combination of tramadol and triclofenac, Applicant's attention is called to the teachings at column 4, lines 29-37, where Raffa teaches that NSAID includes diclofenac. Moreover, throughout the patent, Raffa teaches combining tramadol and an NSAID. Further, in response to Applicant's argument that *Raffa, like Voss et al., provides no indication that there might be any problem arising from the direct combination of tramadol and diclofenac*, it is of note that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Raffa is cited in view of the teachings of Addicks and Bergamini.

Applicant argues that Mok et al. is newly cited as showing that simultaneous administration of tramadal (presumably tramadol) and diclofenac produced superior pain relief. However, Mok et al. does not add any new aspect to the prior art cited so far. Rather, Mok et al. relates to a study that evaluated the analgesic efficacy and safety of the combined use of tramadol and diclofenac. During the course of this study the patients received tramadol *IV* and diclofenac *IM.* The statement that tramadol was given *IV* (intravenously) means that a suitable solution comprising tramadol was introduced directly into a vein. The statement that diclofenac was given *IM* (intramuscularly) means that a suitable solution comprising diclofenac was injected directly into a muscle. Thus, the two active agents were administered separately by entirely different routes of

administration. Indeed, neither tramadol, nor diclofenac was administered orally. Therefore Mok et al. teaches nothing about how to formulate an oral dosage form of tramadol and diclofenac, much less anything about how to prevent formation of a sparingly soluble compound that reduces the bioavailability of the two active substances. As noted, according to Mok et al., tramadol and diclofenac were given via different routes of administration, namely intravenously and intramuscularly. Consequently, these substances were necessarily administered to different parts of the human body and therefore could not form a sparingly soluble compound with one another. Such a situation is not in the least comparable to the administration of both compounds via one and the same oral dosage form. Rather, when an oral dosage form comprising both tramadol and diclofenac is administered, then both tramadol and diclofenac will be present in the gastroenteral tract, which could lead to the formation of sparingly soluble compound between these components. In other words the problem underlying the present invention cannot occur during the study as described in the reference of Mok et al., and Mok et al. provides no help in solving it.

In response to applicant's arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Mok is cited for the suggestions that "the combined use of tramadol and diclofenac produces enhanced analgesic effects which

make it a useful therapeutic regimen in pain management". See Mok at page 132, PI-11.

Applicant argues that Addicks discloses a pharmaceutical dosage form comprising an anticoagulant, such as wafarin, and a platelet inhibiting agent, such as aspirin or some other NSAID, separated by a coating layer. However, Addicks, like Voss et al. and Raffa, does not evidence any awareness or appreciation of the formation of a release-inhibiting sparingly soluble compound by tramadol and diclofenac. Bergamini and Bodley are cited as purportedly disclosing that diclofenac exhibits interaction with a number of active ingredients. However, Bergamini focuses on the combination of diclofenac with tobramycin and does not disclose tramadol, a completely different active ingredient. Bodley discloses the combination of diclofenac with 2-hydroxypropyl beta-cyclodextrin. Bodley also does not disclose the combination of tramadol and diclofenac. None of the references disclose the particular issues associated with the combination of diclofenac and tramadol, including the formulation of a compound with a relatively low solubility.

In response to applicant's arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*,

642 F.2d 413, 208 USPQ 871 (CCPA 1981). Addicks is relied upon for the teachings of a coating to obtain a stable composition of combination of active agents.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. TRAN whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. TRAN/
Primary Examiner, Art Unit 1615